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AN ESTIMATE OF ADULT MORTALITY IN THE UNITED STATES FROM PASSIVE SMOKING

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The purpose of this paper is to estimate the number of adult deaths per year in the United States from passive smoking. The epidemiological literature on passive smoking and adult mortality and cancer and heart morbidity is reviewed. Combined relative risks for lung cancer, cancers other than lung, and heart disease are calculated for each sex and disease category. These data along with estimates of nonsmoker death rates and populations exposed allow calculation of annual deaths in each category. Reduced relative risk and reduced exposure at older ages are taken into account as well as a correction for possible misclassification of smokers as nonsmokers and exposed nonsmokers as nonexposed. Altogether 46,000 deaths per year are calculated consisting of lung cancer (3000) other cancer (11,000) and heart disease (32,000). Reasons why such high estimates for other cancer and heart disease may be possible are explored. It is concluded that exposure to environmental tobacco smoke can have adverse long term health effects that are more serious than previously thought.

Introduction

Several attempts have been made to estimate U.S. adult mortality from passive smoking. For example, Repace and Lowrey (1985) estimated the lung cancer deaths to be about 5000 per year. Fong (1982) estimated total mortality at 10,000 to 50,000. Russell *et al.* (1986) estimated total U.S. mortality at more than 4000. The present estimate is based on epidemiological evidence currently available on lung cancer, cancers other than lung, and heart disease.

The Surgeon General of the United States (USSG, 1986) and the U.S. National Academy of Sciences (NRC, 1986) have issued reports stating that passive smoking can cause lung cancer. In the National Academy report the relative risks from the various lung cancer studies were combined into an overall relative risk using a procedure somewhat similar to that which is used in this work. The Academy report then projects that about 20% of the 12,000 U.S. lung cancer deaths per year among never smokers is due to passive smoking. This is reasonably close to the 3000 per year projected here for never smokers plus exsmokers. The methods used in the National Academy report are further detailed in Wald *et al.* (1986). Blot and Fraumeni (1986) have also presented an overview of studies of lung cancer and passive smoking. They use a method of combining the relative risks from various studies essentially identical to that used here. Thus, the procedure of combining relative risks from various passive smoking studies to obtain overall relative risks and tighter confidence intervals is now well established by authorities in the field. Also, the method used here to calculate annual deaths from the relative risks appears to be validated by the National Academy results for lung cancer. However, both the Surgeon General's task force and that of the National Academy felt that the data, as of 1986, on cancers other than lung and on heart disease were still too meager to allow calculation of reliable overall risks.

Since 1985 considerably new epidemiological information has become available, particularly on heart disease. This new information is reviewed and combined with the old data to calculate updated relative risks, overall confidence limits, and estimated annual U.S. deaths from passive smoking and the three main diseases, namely, lung cancer, cancers other than lung, and ischemic heart disease. The total particulate matter dose retained by passive smokers is too low to account for the health effects of passive smoking if one starts with the health effects exhibited by direct smokers and ratios down from the dose retained by them. Reasons why such a discrepancy might occur are explored.

Methods

Studies to be considered in the analyses were obtained originally from the literature searches of the U.S. Office on Smoking and Health (OSH, 1979–85). More recently, studies have come to light primarily through personal contact with workers in the passive smoking field. Criteria for admitting data to the analysis are:

1. Studies on the association of passive smoking with adult mortality or morbidity from lung cancer, other cancer or ischemic heart disease were included. All cause data were not used because essentially no male data are available. The female data, if calculated, yield overall results that are in the same range as the results derived from the three main diseases (see Appendix B). Emphysema is not included because the nonsmoker death rate is so low that less than 1% of deaths from passive smoking would be predicted from this source (see Appendix B).
2. Retrospective studies should have controls.
3. Observations should be based on spouse exposure or on general exposure of more than 10 years duration. The diseases under study are known to have long induction periods, and it is assumed that most married people old enough to die of passive smoking would have been exposed 20 years or more.
4. Enough data should be available from the study to allow calculation of a weighting factor for combining the relative risks.

Two risk models were used and a third was considered. The primary model used combined relative risks from the various studies that pertained to a given sex and disease and assumed that the combined relative risk was constant with age, although variation with age of the underlying neversmoker death rate and the fraction of the population exposed were included. In the secondary risk model the combined relative risk was also allowed to vary with age. These models were suggested in part by the considerations in James Robins' Appendix D in the National Academy report (NRC, 1986). The third risk model was based on the rate difference between the death rates for exposed and nonexposed populations. A detailed analysis of this model for heart disease in women was carried out (see Appendix C). It was concluded that the relative risk models were much superior to the rate difference model when combining data across different cultures as is the case here where some of the studies are from the orient.

Wherever a study showed both a crude relative risk or odds ratio and an adjusted ratio, the adjusted ratio was used. To obtain a combined relative risk a method similar to that of Blot and Fraumeni (1986) was used. Case control studies were aggregated using Program 2 of Rothman and Boice (1982). Cohort studies were aggregated using Program 7. A combined relative risk for the two aggregates was obtained using:

$$R_{cb} = \exp \frac{w_{co} \ln R_{co} + w_{cc} \ln R_{cc}}{w_{co} + w_{cc}} \qquad (1)$$

where R_{cb}, R_{co}, and R_{cc} are the relative risks for the combined total, the cohort studies, and the case control studies, respectively, and w_{co} and w_{cc} are the weights for the cohort and case control studies, respectively, which are the inverse of the respective variances. Variance is taken as the square of the standard deviation which is equal to $\ln R/\chi$, so the weight, $w = (\chi/\ln R)^2$. The source of these equations is Rothman (1986). Confidence intervals were calculated from a combined $\chi = w^{1/2} \ln R_{cb}$. For some studies it was necessary to calculate a chi from the confidence limits in order to calculate a weight since no other data were available. These data were then combined with the rest using Eq. (1). Ages of death from 35 and up were used and should include essentially all adult deaths from passive smoking. In some studies morbidity relative risks were reported whereas our interest is in mortality. The morbidity relative risks were accepted as surrogates for mortality relative risks because, for cancer, the survival rates for exposed and nonexposed cases appeared to be similar while, for heart disease, incidence relative risks, if anything, are lower than mortality relative risks (Svendsen *et al.*, 1987).

The 1985 smoking status for U.S. residents in 5 year age increments was obtained from the National Center for Health Statistics. Nonsmokers were equated to never smokers plus exsmokers. The fractions of never smokers living with ever smokers (24% for males and 60% for females), all of whom were considered to be exposed, were obtained from controls of the U.S. based studies for all three diseases. These fractions were assumed to hold also for nonsmokers (never plus ex). The fractions of all nonsmokers exposed as nonsmokers living with nonsmokers, but still exposed at home or at work (37% for males and 16% for females), were obtained from Friedman *et al.* (1983). These fractions were assumed to hold for nonsmokers living with never smokers. By adding the two fractions the total nonsmoker exposure of 61% for males and 76% for females was obtained. These overall exposure fractions are known to be higher at younger ages and lower at older ages. The data of Friedman *et al.* (1983) were used to develop smoothed values of fraction exposed 10 years earlier (midpoint of a 20 year exposure) for each sex and 5 year age interval normalized to 61% for males and 76% for females. By multiplying each population element by each fraction exposed element, the exposed population by sex and 5 year age interval could be determined.

Death rates for never smokers for lung cancer by sex and 5 year intervals were drawn from Garfinkel (1981)

and smoothed using a semi-log plot against age. For cancers other than lung for females a semi-log plot of 1984 age specific death rates for ages 35+ was developed for malignant neoplasms less malignant respiratory neoplasms from the data of the National Center for Health Statistics (1986). Then, a parallel plot was developed using as reference points the neversmoker data of Hammond (1966) for ages 45–64 and 65–79 to yield neversmoker rates for ages 35+ for each 5 year age interval. For heart disease never smoker death rates by sex and 5 year age intervals for 1963 were developed from the appendix tables in Hammond (1966). These were reduced to 1984 equivalent rates (with the reduction factors corrected for the effects of smoking) by a technique similar to that used by the U.S. Office of Technology Assessment (OTA, 1985). Semi-log graphs were used to estimate never smoker death rates by 5 year age intervals for the entire age range (see Appendix A, Table A3).

The excess death rate for never smokers for passive smoking (D_{ps}) for each sex, disease and 5 year age range was calculated from the never smoker death rates (D_{ns}) using the formula:

$$D_{ps} = D_{ns}(R - 1)/(F_p(R - 1) + 1) \qquad (2)$$

where F_p is the fraction of the population that is exposed and R is the combined relative risk. This excess death rate was assumed to apply to all nonsmokers. Deaths were then calculated by multiplying the passive smoking excess death rate by the exposed population for each sex and 5 year age interval, and summed. For those calculations where the relative risk was assumed to have varied with age, the excess death rates for passive smoking were recalculated from the age specific relative risks for each 5 year age interval. Additional calculations were carried out to show the effects of bias including those from misclassification of smokers as nonsmokers and exposed nonsmokers as unexposed, using a method similar to that of Wald *et al.* (1986).

Results

Relative risks

The results for passive smoking relative risk for females for lung cancer are shown in Table 1. The three cohort studies are listed first and show a combined relative risk for all exposures including exposures to exsmokers of 1.34. At the time the analysis was made there were fourteen acceptable case control studies with a combined relative risk of 1.50. The overall combined relative risk, based on 1,174 cases, is 1.44 with 95% confidence limits of 1.3–1.7. The male lung cancer observed relative risks are shown in Table 2. There are now nine studies with 144 total cases. The overall combined relative risk is 2.1 with 95% confidence limits of 1.3–3.2. Data excluded from Tables 1 and 2 along with the reasons were the following: Chan *et al.* (1979), current exposure only; Knoth *et al.* (1983), no controls; Kabat and Wynder (1984) nonspouse data, current exposure only; Buffler *et al.* (1984), 0–32 year data, not a minimum of 10 years exposure. A paper by Dalager *et al.* (1986) describes a pooling of data from Correa *et al.* (1983), Buffler *et al.* (1984) and a study of males in New Jersey. They observed an adjusted odds ratio for spouse exposure of 1.47, but since Correa *et al.* (1983), and Buffler *et al.* (1984), were already included in Tables 1 and 2 and since the New Jersey data were not available separately, it was decided to omit the Dalager *et al.* (1986) study from this analysis. Also, available were abstracts of two recent papers. Geng *et al.* (1987) from China with a relative risk of 2.2 and Inoue and Hirayama (1987) from Japan with a relative risk of 2.3, both for females. Also W. K. Lam (1985) in a thesis from the University of Hong Kong that is quoted in Lam *et al.* (1987) found a relative risk of 2.0 for adenocarcinoma among females. These inputs arrived too late to be included in the analysis.

The data of Hirayama (1984a) on female lung cancer are sufficiently detailed to indicate a declining relative risk with age from 1.87 at approximately age 50 to 1.43 at approximately age 75. These data were used to develop a second death calculation assuming a declining relative risk, but still normalized to 1.44. However, Hirayama's data show no such decline in passive smoking relative risk with age for males. Instead, the trend appears to rise with age, so no secondary calculation was made.

There are now five studies relating passive smoking to total cancer or cancer other than lung in females. The individual and combined relative risks for females are shown in Table 3. The total combined relative risk is 1.16. The total cases, 2,933, are two and one-half times the total cases for female lung cancer (Table 1) although 2,505 are concentrated in the large Hirayama (1984a) study. This is a large data base. The total combined chi square is 11 compared to 27 for female lung cancer.

The two largest of the female studies, Hirayama (1984a) and Sandler *et al.* (1985), cover different age of death ranges. Hirayama covers 50 to 80+ while Sandler *et al.* cover <30 to 59. The two studies taken together would indicate a rather sharp decline in relative risk with age from about 3.5 at age 40 to about 1.04 at age 80. The high relative risks at the younger ages may be due to premenopausal breast cancer (see Sandler *et al.*, 1986). Two calculations of U.S. female deaths from passive smoking and other cancers were made, one using the 1.16 relative risk from Table 3 at all ages and one using the declining relative risks.

Gillis *et al.* (1984), Sandler *et al.* (1985), and Reynolds (private communication) also report on other can-

Table 1. Female relative risks for lung cancer from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95% C.L.	Mantel Trend 1-tail p
Cohort Studies:							
Hirayama (1984a)	Japan	200	1.9	0.002	1.6	1.1–2.2	0.002
Garfinkel (1981)	United States	153	1.1	—	1.2	0.8–1.6	—
Gillis *et al.* (1984)	Scotland	8	—	—	1.1	0.2–5.6	
Combined Cohort		361			1.34	1.1–1.7	
Case Control Studies:							
Trichopoulos *et al.* (1983)	Greece	77	2.6	0.19	2.1	1.2–3.6	0.005
Correa *et al.* (1983)	Louisiana	22	3.5	0.02	2.1	0.8–5.2	—
Buffler *et al.* (1984)	Texas	27*	—	—	0.9	0.4–2.3	—
Kabat and Wynder (1984)	United States	24	—	—	0.8	0.3–2.5	—
Sandler *et al.* (1985)	North Carolina	2	—	—	inf	—	—
Garfinkel *et al.* (1985)	United States	116	2.0	0.05	1.3	0.8–1.9	0.025
Wu *et al.* (1985)	California	28*	—	—	1.2	0.5–3.3	—
Lee *et al.* (1986)	United Kingdom	32	—	—	1.0	0.4–2.7	—
Akiba *et al.* (1986)	Japan	94	2.1	—	1.5	0.9–2.6	0.06
Koo *et al.* (1987)	Hong Kong	86	1.2	—	1.6	0.9–3.1	—
Pershagen *et al.* (1987)	Sweden	67	3.2	—	1.2	0.7–2.1	0.12
Humble *et al.* (1987)	New Mexico	20	1.2	—	2.3	0.9–6.6	—
Brownson *et al.* (1987)	Colorado	19	—	—	1.7	0.4–3.0	—
Lam *et al.* (1987)	Hong Kong	199	—	—	1.65	1.2–2.4	
Combined Case Control		813			1.50		1.3–1.8
Combined Cohort and C/C		1174			1.44	1.26–1.66	

* Private communication.
†From Blot and Fraumeni (1986).

cer in males. The relative risks were 0.6, 1.5 and near unity, respectively. The number of cases in each study is very small with no statistical significance. Therefore, it was decided to use a neutral relative risk of 1.0 for males for cancer other than lung until more data become available.

There are now six studies of passive smoking and heart disease in females. The individual and combined relative risks are shown in Table 4. Studies new since 1985 are Lee *et al.* (1986), Martin *et al.* (1986a) and the important, large Helsing *et al.* (1988) paper from Maryland. The overall combined relative risk based on 1,622 cases is 1.23 with 95% confidence limits of 1.11 to 1.36 and a combined chi square of 16. Helsing *et al.* (1988) and Martin *et al.* (1986a) provide data for younger women and indicate high relative risks (average 2.45)

Table 2. Male relative risks for lung cancer from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95% C.L.	Mantel Trend 1-tail p
Cohort Studies							
Hirayama (1984a)	Japan	64	2.3	0.16	2.25	1.11– 4.9	0.023
Gillis *et al.* (1984)	Scotland	6	—	—	3.3	0.7 –16.5	—
Combined Cohort		70			2.5	1.2 – 5.0	
Case Control Studies:							
Correa *et al.* (1983)	Louisiana	8	—	—	2.0	0.4 –10	—
Buffler *et al.* (1984)	Texas	8*	—	—	1.6	0.3 – 8.1	—
Kabat and Wynder (1984)	United States	12	—	—	1.0	0.3 – 3.2	—
Lee *et al.* (1986)	United Kingdom	15	—	—	1.3	0.4 – 4.6	—
Akiba *et al.* (1986)	Japan	19	—	—	1.8	0.5 – 5.6	—
Humble *et al.* (1987)†	New Mexico	8	—	—	4.2	1.0 –16.8	—
Brownson *et al.* (1987)†	Colorado	4			2.7	0.2 –31	—
Combined Case Control		74			1.8	1.0 – 3.3	—
Combined Cohort and C/C		144			2.1	1.3 – 3.2	

*Private Communication.

Table 3. Female relative risks for cancer other than lung from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95% C.L.	Mantel Trend 1-tail p
Cohort Studies:							
Hirayama (1984a)*	Japan	2505	1.16	0.01	1.11	1.0 –1.2	0.05
Gillis *et al.* (1984)	Scotland	43	—	—	1.2	0.6 –2.5	—
Reynolds *et al.* (1987)	California	70†	—	—	1.7	1.1 –2.7	—
Combined Cohort		2618			1.13	1.03–1.24	—
Case Control Studies:							
Miller (1984)†	Pennsylvania	84	—	—	1.25	0.7 –2.3	—
Sandler *et al.* (1985)	North Carolina	231	—	—	2.0	1.3 –2.9	—
Combined Case Control		315			1.7	1.2 –2.45	
Combined Cohort and C C		2933			1.16	1.06–1.27	

*Obtained by subtracting data for lung cancer from data for all sites.
†Provided by Dr. Reynolds.
‡Age adjusted Mantel-Haenszel values for nonemployed wives.

for ages up to about 50. At higher ages there is no trend with an average relative risk of 1.17 holding out to age 84.

For male heart disease and passive smoking there are now four studies (see Table 4). The two new ones are Lee *et al.* (1986) and Helsing *et al.* (1988). The result of Svendsen *et al.* (1987) is shown for information, but is not used in calculating the combined relative risk because it pertains to a high risk group. The combined relative risk based on 443 cases is 1.31 with 95% confidence limits of 1.1 to 1.6 and a combined chi square of 9. The results are remarkably uniform. As in the female data the relative risk is high at the younger ages, about 2.9, but declines to a nontrend average of 1.28 which extends from age 55 out to the older ages. Svendsen *et al.* (1987) show that there was very little difference between never smoking men married to nonsmokers and those married to smokers in the major coronary risk factors such as baseline blood pressure, total cholesterol, and LDL cholesterol. This work was reported in more detail in Martin *et al.* (1986b). Small differences were found in weight (195 vs. 190 if wives were smokers) and drinks per week (10 vs. 8 if wives were smokers). On the other hand, Garland *et al.* (1985)

Table 4. Relative risks for heart disease from passive smoking

	Locale	Total Cases	Highest Exposure RR	Highest Exposure 2-tail p	All Exposures RR	All Exposures 95% C.L.	Mantel Trend 1-tail p
Females							
Cohort Studies:							
Hirayama (1984b)	Japan	494	1.3	0.038	1.16	0.9– 1.4	0.02
Gillis *et al.* (1984)	Scotland	21	—	—	3.6	0.9–13.8	—
Garland *et al.* (1985)	California	19	—	—	3.5	0.9–13.6	—
Helsing *et al.* (1988)	Maryland	988	1.27	—	1.24	1.1– 1.4	0.005*
Combined Cohort		1522			1.23	1.1– 1.4	
Case Control Studies:							
Lee *et al.* (1986)	United Kingdom	77	—	—	0.9	0.7– 1.3	—
Martin *et al.* (1986a)	Utah	23	—	—	2.6	1.2– 5.7	—
Combined Case Control		100			1.29	0.8– 2.0	
Combined Cohort and C/C		1622			1.23	1.1– 1.4	
Males							
Cohort Studies:							
Gillis *et al.* (1984)	Scotland	32	—	—	1.30	0.7– 2.6	—
Lee *et al.* (1986)	United Kingdom	41	—	—	1.24	0.5– 2.6	—
Helsing *et al.* (1988)	Maryland	370	—	—	1.31	1.1– 1.6	—
Combined Cohort		443			1.31	1.1– 1.6	—
Svendsen *et al.* (1987)†	United States	13	—	—	2.2	0.7– 6.9	—

*Based on Cochran chi-square of 9.2.
†MRFIT cohort of high risk individuals, included for information only.

found that never smoking women married to smokers had slightly lower weight, slightly lower blood pressure, and slightly higher cholesterol, all nonsignificantly different, versus never smoking women married to never smokers. All of these authors conclude that the increased passive smoking risks they observed cannot be ascribed to differences in the major coronary risk factors between passively exposed and nonexposed never smokers.

It is impressive that the relative risks for heart disease from passive smoking rise in an orderly manner from the lowest risk group, Japanese women at 1.16, through American women at 1.27, and American men at 1.31, to high risk American men at 2.2.

A correction for misclassification was attempted for all three disease categories. Following Wald *et al.* (1986), and presuming that the passive smoking studies were done somewhat more carefully than the general questionnaire studies they cite, it was assumed that 5% of ever smokers were misclassified as never smokers. Along with Wald *et al.* (1986) we assumed that the nonexposed nonsmokers were actually exposed to 1/3 the extent of the exposed nonsmokers except that for Greece, Japan, and Hong Kong, where less than 30% of women had ever smoked, the correction for nonexposed female nonsmokers was omitted. It is believed that older, nonsmoking women in Greece and Japan, and probably in Hong Kong also, because of their social habits, were exposed to relatively little tobacco smoke beyond that of their husband's. Since most of the misclassified smokers were found to be light smokers or longstanding exsmokers, reduced relative risks for the misclassified ever smokers were calculated, as noted in Appendix A. The modified passive smoking relative risks are shown in Table 5. The false relative risks due to smoker misclassification are somewhat lower than calculated earlier by Wells (1986) because of the assumption of light smokers and long term exsmokers among those misclassified, following Wald *et al.* (1986), and the use of a more accurate formula. In general, the misclassification of smokers has a large negative effect on male relative risk which is more or less offset by the positive effect of exposure of the "nonexposed." For females the smoker misclassification effect is small to negligible, but because the relative risks are smaller and no correction was made to "eastern" data (Japan, Greece, and Hong Kong), the positive effects of exposure of "nonexposed" are also smaller.

Calculation of Deaths

The details for the calculation of female lung cancer deaths from the relative risks, both constant and declining, are shown in Table 6 as an example. Similar calculations were made for the other disease and sex categories and are shown in Appendix A. The results of all of the calculations are summarized in Table 7. These results are restated per million total population in Table 8. Where the relative risk appears to decline with age and where neversmoker death rates at the younger ages are low, as in female heart disease and lung cancer, there is a reduction in mortality calculated by using the age specific relative risks. Otherwise, the higher exposed population at the younger ages outweighs the higher death rate at older ages and total mortality is increased. In terms of total deaths the effects of using age specific relative risks tend to cancel out. The total deaths, before adjustment for misclassification, for both males and females are about 19,500 for a total for both sexes of about 39,000.

The effects of misclassification on total deaths are substantial, raising the total to 53,000. Most of this increase is in heart disease where the numbers are large and the effects of smoker misclassification, although not necessarily small, are still heavily outweighed by the partial exposure of the "nonexposed."

To be conservative a best estimate for passive smok-

Table 5. Passive smoking relative risks modified for misclassification.

	Lung Cancer	Other Cancer	Heart Disease
Females			
1. Combined relative risk.	1.44	1.16	1.23
2. False relative risk due to projected 5% smoker misclassification.	1.01	1.002	1.01
3. Combined relative risk corrected for smoker misclassification, (1) ÷ (2).	1.43	1.16	1.22
4. (3) corrected for exposure of "nonexposed" at 1/3 that of exposed.	1.48	1.21	1.32
Males			
1. Combined relative risk.	2.1	1.0*	1.31
2. False relative risk due to projected 5% smoker misclassification.	1.3	—	1.11
3. Combined relative risk corrected for smoker misclassification, (1) ÷ (2).	1.6	—	1.17
4. (3) corrected for exposure of "nonexposed" at 1/3 that of exposed.	2.4	—	1.29

*Assumed value for lack of better data.

Table 6. Annual U. S. female lung cancer deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 1.44		Relative Risk Declining	
					Excess Death Rate	Deaths	RR	Deaths
35–39	1.6	6150	0.94	5781	0.50	29	1.70	39
40–44	2.4	4622	0.92	4252	0.75	32	1.69	43
45–49	3.6	3846	0.89	3423	1.14	39	1.68	52
50–54	5.3	3856	0.87	3355	1.69	57	1.62	72
55–59	7.8	4161	0.84	3495	2.51	88	1.56	104
60–64	11.0	4192	0.77	3228	3.62	117	1.49	126
65–69	16.6	4160	0.70	2912	5.55	162	1.43	159
70–74	23.5	3441	0.59	2030	8.21	167	1.36	142
75–79	34	3004	0.49	1472	12.3	181	1.29	127
80–84	46	1886	0.29	547	18.0	98	1.18	43
85+	52	1003	0.10	100	21.9	22	1.08	4
Totals	13.0	40291	0.76	30595	3.0	992	—	911

ing deaths might be 46,000, halfway between the 39,000 calculated directly from the relative risks and the 53,000 calculated using the modified relative risks. By disease the total would consist of 3,000 lung cancer, 11,000 other cancer, and 32,000 heart disease. For each million of total population the deaths by disease would be 13 for lung cancer, 46 for other cancers, and 134 for heart disease. These numbers may be useful for populations similar to that of the United States in terms of proportions of never smokers, exsmokers, and smokers, and in terms of the proportion of the population that is less than 35 relative to that over 35. For other populations the per million numbers are best not used, but the methodology can be used. That cancer other than lung and heart disease are legitimate contributors to deaths from passive smoking is supported in Hirayama, (1984a,b) in his large prospective study. He found significantly elevated risks for all three diseases, and his result for lung cancer is now believed to be valid, (USSG 1986; NRC, 1986). It is difficult to believe that his lung cancer result is valid while the other two are not.

Discussion

The cancer sites for passive smoking appear to differ somewhat from those for direct smoking. Using information on specific cancer sites from Dr. Hirayama (private communication) it appears that cancers common to both types of smoking are lung, liver, cervix, nasal sinus, and leukemia. Some of these cancers are only weakly associated with direct smoking. Cancers associated to some degree with direct smoking, but absent in passive smoking are buccal cavity, pharynx, larynx, esophagus, stomach (Hirayama, 1984a), urinary bladder (Kabat *et al.*, 1986), kidney and pancreas. Cancers related to passive smoking, but absent in direct smoking are brain (Hirayama, 1984a), endocrine glands (Sandler *et al.*, 1985), lymphoma and breast (Sandler *et al.*, 1985, 1986; Hirayama, private communication). The first three are significant at the 95% level. The combined breast relative risk of 1.4 is significant at only 88%. Higher relative risks for these four sites might be found for direct smoking if epidemiologists used nonpassively

Table 7. Summary: U.S. annual deaths from passive smoking

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk.	992	8599	9768	19359
2. Relative risk declining with age.	911	11165	7602	19678
3. (1) corrected for misclassification.	1232	12280	14995	28507
Males:				
1. Constant combined relative risk.	1606	0	17335	18941
2. Relative risk declining with age.	1606	0	18164	19770
3. (1) corrected for misclassification.	2499	0	22467	24966
Totals for both sexes:				
1. Constant combined relative risk.	2598	8599	27103	38300
2. Relative risk declining with age.	2517	11165	25766	39448
3. (1) corrected for misclassification.	3731	12280	37462	53473
Best current estimate, both sexes (rounded).	3000	11000	32000	46000

Table 8. Summary: Deaths per million population in U.S. from passive smoking. (based on 239,000,000 U.S. population in 1985).

	Lung Cancer	Other Cancer	Heart Disease	Total
Females:				
1. Constant combined relative risk.	4.15	35.98	40.87	81.00
2. Relative risk declining with age.	3.81	46.71	31.81	82.33
3. (1) corrected for misclassification.	5.15	51.38	62.74	119.27
Males:				
1. Constant combined relative risk.	6.72	0	72.53	79.25
2. Relative risk declining with age.	6.72	0	76.00	82.72
3. (1) corrected for misclassification.	10.46	0	94.00	104.46
Totals for both sexes:				
1. Constant combined relative risk.	10.87	35.98	113.40	160.25
2. Relative risk declining with age.	10.53	46.71	107.81	165.05
3. (1) corrected for misclassification.	15.61	51.38	156.74	223.73
Best current estimate, both sexes (rounded).	13	46	134	193

exposed never smokers as the referrent category rather than all never smokers as is usually done. Another difference between passive smoking and direct smoking is that the ratio of lung cancer deaths to deaths from other cancer for females or from heart disease for both sexes is much lower in passive smoking than in direct smoking.

These differences in mortality effects are probably real and reflect differences in chemistry and physics between direct smoking and passive smoking. Environmental tobacco smoke is generated in the burning tip of the cigarette at a lower temperature than direct smoke and therefore contains higher proportions of complicated organic compounds that tend to be carcinogenic (Brunnemann *et al.*, 1978). More importantly, (see Appendix D) the mainstream smoke, although generated at a particle size of about 0.7 μm, is very concentrated and appears to agglomerate into larger particles. Deposition rates are high, about 80%. Deposition occurs primarily in the mouth or in the larger airways of the lung where the particles are cleared relatively quickly into the mouth. This material is then swallowed. Some of it may be eliminated and produce no health effects at all or it may cause the digestive type cancers observed. Only a portion of mainstream smoke appears to remain as small particles that can penetrate deeply into the alveolar region. Environmental tobacco smoke, on the other hand, is very dilute, with a mass median diameter of about 0.4 μm. Particles in this size range have very low deposition rates, on the order of 10%, but what does deposit does so deep in the alveolar region of the lung where clearance times are longer. Black and Pritchard (1984) estimate that cigarette tar has a 17 hour half-time rate of clearance from the alveolar region, much longer than clearance times from the ciliated parts of the lung, but much shorter than for inert particles. This means that smoke particles are very likely dissolving in the fluids in the alveolar region and are being cleared into the blood and lymph systems for circulation throughout the body.

In summary, there are two types of smoking: (a) large particle smoking, or its equivalent, which is the major component of direct smoking, which results in massive deposition in the mouth and larger airways of the lung, rapid clearance, cancers of the mouth, central lung and digestive system, and possibly heart disease, and (b) small particle smoking, which is a minor component of direct smoking, but the entirety of passive smoking, and which results in low doses deep in the lung, slow clearance, some lung cancer, but primarily other cancers and adverse heart effects.

These differences in chemistry and physics also explain, at least in part, the rather high mortality observed for passive smoking relative to the deposited dose of particulate. Smoke retention by a passive smoker is only about 1/400 that retained by a direct smoker in a 16 hour day (0.64 mg for the passive smoker per USSG (1986, p. 196) and 240 mg for the direct smoker assuming twenty 15 mg tar cigarettes and 80% retention). In comparison, the ratio of lung cancer death rates is about 1/35. For cancers other than lung in females the ratio is about 1/7, for heart disease in females about 1.14 and for heart disease in males about 1/3. Preliminary calculations which are shown in Appendix D indicate that the smoke retained deep in the alveolar region may have a dose ratio higher than 1/400, perhaps as high as 1/60. It may be that carcinogenic material that solubilizes and clears from the alveoli into the blood may cause not only some of the cancers other than lung that are observed in passive smoking, but also some of the heart disease from passive as well as direct smoking. The hypothesis of Benditt and Benditt (1973) that arterial plaques are caused by DNA-modifying agents is receiving increasing support. See, for example, the recent work of Penn *et al.* (1986) on cell transforming capability of human atherosclerotic plaque DNA and the earlier work of Albert *et al.* (1977) and Penn *et al.* (1981) on the formation of arterial plaques in cockerels with dimethylbenz(α)anthracene and benzo(α)pyrene.

Another possible factor that might help explain the disparate mortality effects versus dose is the level of disease susceptability in passive smokers versus direct

smokers. The median age for passive smoking death from lung cancer for males is 66 and the deaths constitute 0.006% per year of the exposed population. The first 0.006% of male smokers have died of lung cancer by age 46 at which age the lung cancer death rate is doubling every four years. At age 66 the smoker lung cancer death rate is doubling about every 13 years. In other words, in passive smoking deaths we are dealing with only the very most susceptible people, whereas in direct smoking most of the victims are much nearer average susceptibility. Similar considerations apply to the other diseases here discussed.

A question often raised is that direct smokers are also passive smokers, so why do they not get the passive smoking related cancers. We have already pointed out that the use of nonexposed never smokers as the referrent category for smoker relative risk would increase the apparent risk for smokers. Another possible explanation is the probability of competing risks. Most of the highly susceptible direct smokers would have died in their forties or fifties from smoking related disease and would not be available to die of passive smoking related disease in their sixties or seventies.

The passive smoking mortality calculated in this study, namely, 46,000, may be low. Repace and Lowrey (1985) calculate lung cancer deaths from passive smoking at 4,665, or about 50% higher than our estimate, primarily because of postulated intense exposure at the workplace, a factor not taken into account in this study since the relative risks are based largely on home exposure. If Repace and Lowrey are correct, the higher exposure would lead to corresponding increases in deaths from heart disease and other cancer. Also, only ischemic heart disease is considered here. As the all cause data in Appendix B indicate, other cardiovascular diseases and diabetes may be sensitive to environmental tobacco smoke and may increase the total deaths.

The new epidemiological studies on passive smoking support the earlier ones and indicate that not only lung cancer, but other cancer and heart disease are serious problems. In fact, lung cancer appears to be only the tip of the iceberg. To be on the safe side public health policy should be to protect nonsmokers from environmental tobacco smoke.

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Table A1. Annual U.S. male lung cancer deaths from passive smoking

Age of Death	Neversmoker Death Rate per 100,000	Nonsmoker Population 1000's	Fraction Exposed	Exposed Population 1000's	Relative Risk Constant at 2.1	
					Excess Death Rate	Deaths
35–39	1.8	5156	0.74	3815	1.09	42
40–44	2.9	4136	0.72	2980	1.78	53
45–49	4.5	3477	0.70	2440	2.80	68
50–54	7.0	3431	0.66	2260	4.46	101
55–59	11	3423	0.63	2155	7.15	154
60–64	16	3489	0.59	2054	10.7	219
65–69	23	3150	0.54	1695	15.9	269
70–74	33	2443	0.45	1099	24.3	267
75–79	49	1712	0.37	633	38.3	242
80–84	72	921	0.27	249	61.1	152
85+	95	516	0.08	41	96.0	39
Totals	15.9	31844	0.61	19420	8.26	1606

Appendix A

Details of death calculations

Tables A1 and A2 show the details of the death calculations for male lung cancer and female cancer other than lung and are similar in all respects to Table 6 in the text except that no declining relative risk calculation is shown for male lung cancer since the evidence that was available (Hirayama, 1984a) indicated no such decline.

In Table A3 the details are given for the development of the never smoker relative risks for heart disease that were used in the death calculations. As noted in the text, the 1963 neversmoker heart death rates by 5-year intervals were obtained by dividing the never smoker coronary heart deaths in Hammond's (1966) appendix, Table 14, by the person years in his appendix tables 2a and 2b. Reduction factors to account for the change in heart death rates between 1963 (end of Hammond's study) and 1984 were then developed by 10 year age intervals from the age specific heart death rates in table 24 of Health U.S. 1986 (NCHS, 1986). These reduction factors were modified for the fractions thought to be due to smoking which were taken from a staff report of the Office of Technology Assessment (OTA, 1985) to yield a combined never smoker reduction factor, interpolated back to 5-year age intervals, for application to the Hammond never smoker death rates. These modified rates, which are for enrollment age and therefore about 2 years younger than age of death, were then plotted against age of death on semi-log graph paper. Trend lines were then drawn through the female and the male points to yield the values in the last column of Table A3.

Tables A4 and A5 are simply the details of the heart death calculations as in Tables 6, A1, and A2 for cancer.

The deaths shown in Table 7 resulting from the corrections for misclassification were calculated from the relative risks in lines 4 of Table 5 taken as constant over the age range. The modification of the observed relative risks for smoker misclassification as shown in Table 5 are based on misclassified smoker relative risks calculated as follows. Based on as yet unpublished work of Wells on misclassification it was assumed that self-reported current smoker relative risks for male and female lung cancer in the U.S. and U.K. were 11 and 7, and 4.6 and 2.7 for male and female current smokers in Japan

Table A2. Annual U.S. female deaths from cancer other than lung from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1.16		Relative Risk Declining	
			Excess Death Rate	Deaths	RR	Deaths
35–39	28	5781	3.9	225	4.5	1321
40–44	48	4252	6.7	285	2.9	1411
45–49	80	3423	11.2	383	2.0	1449
50–54	125	3355	17.6	589	1.56	1579
55–59	190	3495	26.8	937	1.30	1591
60–64	265	3228	37.7	1219	1.18	1352
65–69	355	2912	51.1	1487	1.12	1144
70–74	470	2030	68.7	1395	1.08	729
75–79	600	1472	89.0	1310	1.05	431
80–84	750	547	114.7	627	1.034	138
85+	900	100	141.7	142	1.022	20
Totals	256	30595	28.1	8599		11165

Table A3. Development of 1984 neversmoker heart death rates versus age.

Age Range	Death rates from Hammond (1966) at enrolled age per 100,000	Decline in heart DR's % 1963–84	Fraction of decline due to smoking	1984 Neversmoker Death Rate as % of 1963 (smoothed)	Hammond's N.S. D.R. corrected for decline	1984 Neversmoker heart death rate by age of death
Females:						
35–39	7.1	48	0	49	3.5	2.0
40–44	14.1			55	7.7	4.4
45–49	20.4	37	0	60	12.2	10.2
50–54	45.5			63	28.7	23
55–59	104	36	0	64	66	51
60–64	243			64	156	113
65–69	475	37	0	64	304	240
70–74	961			64	615	480
75–79	1648	35	0	65	1072	870
80–84	2774			70	1942	1550
85+	—	21	0	79	—	2770
Males:						
35–39	0	48	50	76	0	20
40–44	79.5			77	61	36
45–49	85.5	42	50	78	67	68
50–54	220			77	169	128
55–59	397	37.5	25	75	298	237
60–64	741			75	556	412
65–69	1089	32	25	76	827	730
70–74	1936			76	1472	1150
75–79	2639	25	10	77	2024	1850
80–84	4374			81	3543	2950
85+	—	14	10	86	—	4700

(Hirayama, 1984a). The 5% of ever smokers who were assumed misclassified as never smokers were assumed to consist of 23% light current smokers and 77% long term exsmokers. The excess risks for current, self-reported smokers were reduced by 2/3 to yield relative risks for misclassified current smokers and by 11/12 for relative risks of misclassified exsmokers essentially as was done by Wald *et al.* (1986). This resulted in misclassified ever smoker relative risks of 2.4, and 1.85 for males and females in the U.S. and U.K. and 1.5 and 1.25 for Japan. Worldwide misclassified smoker relative risks were then calculated to be 1.8 for males and 1.6 for females based on the proportion of "western" and "eastern" cases. The false relative risks shown on lines 2 in Table 5 were then calculated using the formulae in Wells' unpublished work.

For female cancer other than lung, the smoker relative risk of 1.05 was taken from Hammond (1966) and used as is since the effect is too small to make any difference. For ischemic heart disease the ever smoker relative risks from Hammond

Table A4. Annual U. S. female heart deaths from passive smoking.

Age of Death	Neversmoker Death Rate per 100,000 (Table A3)	Exposed Population (Table 6) 1000's	Relative Risk Constant at 1.23		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35–39	2.0	5781	0.38	22	4.0	91
40–44	4.4	4252	0.84	36	2.0	97
45–49	10.0	3423	1.91	65	1.32	85
50–54	23	3355	4.4	148	1.17	114
55–59	51	3495	9.8	344	1.17	265
60–64	113	3228	22.1	713	1.17	548
65–69	240	2912	47.7	1385	1.17	1062
70–74	480	2030	97.2	1973	1.17	1505
75–79	870	1472	180	2647	1.17	2010
80–84	1550	547	334	1828	1.17	1374
85+	2700	100	607	607	1.17	451
Totals	291	30595	31.9	9768		7602

Table A5. Annual U. S. male heart deaths from passive smoking

Age of Death	Neversmoker Death Rate per 100,000 (Table A3)	Exposed Population (Table A1) 1000's	Relative Risk Constant at 1.31		Relative Risk Declining	
			Excess D.R.	Deaths	RR	Deaths
35–39	20	3815	4.9	187	5.2	780
40–44	36	2980	8.9	265	3.0	879
45–49	68	2440	16.9	411	1.92	929
50–54	128	2660	32.1	724	1.42	951
55–59	237	2155	59.8	1289	1.28	1201
60–64	412	2054	105	2157	1.28	2009
65–69	730	1695	189	3195	1.28	2972
70–74	1150	1099	304	3341	1.28	3103
75–79	1850	633	500	3162	1.28	2933
80–84	2950	249	819	2039	1.28	1887
85+	4700	41	1377	565		520
Totals	521	19420	89.3	17335		18164

(1966) were taken as 2.3 for males and 2.0 for females. The excess risks were reduced by 2/3 to yield relative risks for misclassified ever smokers of approximately 1.4 for males and 1.3 for females. These were used worldwide with Wells' unpublished formulae to calculate the false heart disease relative risks shown on lines 2 of Table 5.

Appendix B

Relative risks for all causes of death and for emphysema and chronic obstructive lung disease

Data relating all causes of death with passive smoking for females have been reported for four prospective studies totalling 9537 cases as shown in Table B1. The combined relative risk is 1.165 with 95% confidence limits of 1.11 to 1.22. The only male data available are 75 cases from Gillis *et al.* (1984) with a relative risk of 1.0 so no male analysis was made.

The calculation of the total number of female deaths from all causes for passive smoking is shown in Table B2. The total, 34,164, is considerably larger than the total for cancer plus heart of 19,359 shown in Table 7. Some of the difference is due to uncertainties in the calculations, but other causes of death that might contribute to the all cause total, based on data in a private communication from Dr. Hirayama, are cerebrovascular disease, other heart disease, diabetes, and ulcer.

Hirayama (private communication, also reported preliminarily at 5th World Conference on Smoking and Health, Winnipeg, 1983) provides data relating deaths from emphysema with passive smoking in women. His relative risk, based on 106 cases is 1.3 with 95% confidence limits of 0.85 to 2.05. Kalandidi *et al.* (1987) report incidence data for chronic obstructive lung disease based on 103 cases with an adjusted relative risk of about 1.4. Lee *et al.* (1986) report incidence data for chronic bronchitis from spouse exposure. Based on 17 cases the adjusted relative risk is 1.22. A weighted average of these three relative risks would be about 1.35. The only neversmoker death rate we have is from Hammond (1966) for emphysema at 2×10^{-5}. Assuming 76% exposure, the excess death rate for passive smoking using Eq. (2) would be 0.55×10^{-5} and the total deaths for an exposed population of 30.6 million would be about 170. Even if this number is doubled to take into account deaths from forms of chronic obstructive lung disease other than emphysema, it is still far below the total for cancer and ischemic heart disease.

Table B1. Female relative risks for all causes of death from passive smoking

	Locale	Total Cases	All Exposures		Mantel Trend
			RR	95% C.L.	1-tail p
Cohort Studies:					
Hirayama (1987)	Japan	9106	1.17*	1.12–1.23*	0.000001
Gillis *et al.* (1984)	Scotland	102	1.45	0.91–2.30	—
Garland *et al.* (1985)	California	79	1.06	0.65–1.73	—
Vandenbroucke *et al.* (1984)*	Holland	250	0.79	0.57–1.09	—
Combined Chort:		9537	1.165	1.11–1.22	

*Dr. Hirayama (private communication) provided the data necessary to calculate these items.

*Data from 25 year follow up. Relative risk was 0.89 (0.50–1.62) for 15 year follow up. This study is weak in that exsmoking women were included among the "nonsmokers," and nonsmoking women exposed to exsmoker husbands were included in the "nonexposed." The weakness of the study is emphasized in that the smoking women had a lower overall death rate (33.4%) than the nonexposed nonsmokers (38.1%).

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Table B2. Annual U.S. female deaths from all causes from passive smoking

Age Range	Neversmoker Death Rates from Hammond (1966) at enrolled age per 100,000	Decrement due to heart death rate 1963–84 per 100,000	Corrected Neversmoker death rate at enrolled age per 100,000	Neversmoker death rate corrected to age of death per 100,000	Population exposed 1000's	Fraction of population exposed	Relative Risk Constant at 1.165 Excess D.R.	Deaths
35–39	136	3.6	132.4	120	5781	0.94	17.1	991
40–44	178	6.4	171.6	155	4252	0.92	22.2	944
45–49	254	8.2	245.8	212	3423	0.89	30.5	1044
50–54	352	16.8	335.2	300	3355	0.87	43.3	1452
55–59	561	38	523	445	3495	0.84	64.5	2254
60–64	867	87	780	675	3228	0.77	98.8	3190
65–69	1492	171	1321	1070	2912	0.70	158.3	4609
70–74	2585	346	2239	1830	2030	0.59	275.2	5586
75–79	4790	576	4214	3250	1472	0.49	496.1	7303
80–84	8408	832	7576	6000	547	0.29	944.8	5168
85+	—	—	—	10,000	100	0.10	1623	1623
Totals					30595		111.7	34164
Deaths per million total population								143

Lee *et al.* (1986) report data on chronic bronchitis life long nonsmoking in males exposed to a smoking spouse. Based on nine cases the adjusted relative risk was 0.34. However, for general exposure (4 cases) a positive relative risk was observed. No analysis of these data was attempted.

Appendix C

Rate difference model for assessing female ischemic heart deaths from passive smoking

A rate difference or absolute risk model was investigated for female ischemic heart disease in order to compare it to the relative risk models in ability to translate experience from one type of culture to another. Female ischemic heart disease was chosen because considerable data exist and because heart disease is the largest contributor to total deaths. Also, the relative risk model seems already to be well established for lung cancer (Wald *et al.*, 1986; Blot and Fraumeni, 1986) so a comparison in another disease category appeared to be appropriate.

Data from the four cohort studies (see Table 4) were combined using the direct pooling equations described on page 183 in Rothman (1986). The two case/control studies were omitted. Although their combined rate difference was essentially the same as that for the cohort studies, no good way could be found to combine it with that from the cohort studies. Death rates for exposed and not exposed populations were obtained by dividing the observed deaths in each category by person years which were equated to the mid-point populations multiplied by the years of followup. The rate difference was then obtained by subtracting the nonexposed death rate from the exposed death rate. Variances and weights were calculated by Rothman's formulae. The combined rate difference was obtained by summing the weighted rate differences and dividing by the sum of the weights. Confidence limits (95%) were equated to the rate difference ± 1.96 (variance)$^{1/2}$.

The results of these calculations are summarized in Table C1. The cohort data were also combined using Program 7 of Rothman and Boice (1982) with results essentially identical to those shown in Table C1 for direct pooling. The relative heterogeneity of the relative risks (RR) vs. the rate differences (RD) can be approximated by considering the range of RR-1 versus the range of RD. The range of RR-1 is from 0.16 to 2.6 for a factor of 16.3. The range of the rate differences is 3.7 to 262 or a factor of 71. The ratio for the two large studies, Helsing *et al.* (1988) and Hirayama (1984b), for RR-1 is 0.24/0.16 = 1.5 and for RD is 20.7/3.7 = 5.6. The 95% confidence limits for the rate ratio combination is tighter than for the rate difference combination. Also, the Hirayama study dominates the rate difference aggregation much more than in the rate ratio aggregation, providing 64% of the combined weight (last column of Table C1) in the rate difference case vs. only 17% of the combined weight in the rate ratio case.

Table C1. Rate difference calculations for female ischemic heart disease.

	Total Cases	Relative Risk from Table 4 RR	95% C.L.	Rate difference × 10^5 RD	95% C.L.	Weights for RD × 10^{-5}	RD × weight × 10^{-5}
Cohort Studies:							
Hirayama (1984b)	494	1.16	0.9– 1.4	3.7	−2.1– 9.6	1110	41.4
Gillis *et al.* (1984)	21	3.6	0.9–13.8	169.1	30.7–307.6	2	3.4
Garland *et al.* (1985)	19	3.5	0.9–13.6	262.2	36.0–488.4	0.8	2.0
Helsing *et al.* (1988)	988	1.24	1.1– 1.4	20.7	−0.2– 41.6	88	18.2
Combined Cohort	1522	1.23	1.1– 1.4	5.4	−0.2– 11.1	1201	65.0

Table D1. Regional particle deposition from mouth breathing of side stream smoke

Aerodynamic diameter μm	Cube of diameter	Relative concentration[a]	Relative Volume (Weight) per 0.1μm	Mass Distribution %	Fraction of inhaled particle mass deposited[b]			Mass deposited as % of total mass inhaled
					mouth throat	tracheo-bronchial	alveolar	
0.20	.008	1.5	0.006	0.3	0	0	0.13	0.04
0.25	.016	6.5	0.051	2.4	0	0	0.122	0.29
0.30	.027	10.0	0.135	6.4	0	0	0.115	0.74
0.35	.043	13.0	0.280	13.2	0	0	0.108	1.43
0.40	.064	13.0	0.416	19.6	0	0	0.10	1.96
0.45	.091	6.5	0.296	14.0	0	0	0.105	1.47
0.50	.125	3.5	0.328	15.5	0	0	0.11	1.71
0.60	.216	1.25	0.270	12.7	0	0	0.115	1.46
0.70	.343	0.5	0.172	8.1	0	0	0.12	0.97
0.80	.512	0.25	0.128	6.0	0	0	0.13	0.78
0.90	.729	0.05	0.036	1.7	0	0	0.14	0.24
1.00	1.0	0	0	0	0	0	0.15	0.00
			2.118	99.9				11.08

[a]From Hiller *et al.* (1982), Fig. 1.
[b]From Heyder (1984), Table 1, 250 cm³/second mean flow rate, 4 second breathing cycle.

This domination of the rate difference model by the Japanese study is evident from some rough death calculations. Use of the combined rate difference (5.4×10^{-4}) with the exposed female population from Table A4 (30.6 million) yields total deaths of 1,652 compared with 9,768 calculated from the constant rate ratio model. When the rate differences are plotted against age of death and weighted accordingly it is found that the "western" rate differences increase sharply with age whereas the Japanese rate difference stays constant at about 4×10^{-4}. Constructing a weighted average of these "western" and "eastern" death rates for each of the 5 year age ranges and multiplying by the corresponding exposed populations yields a total of about 2,100 deaths compared with 7,602 in the second relative risk model. Use of the Japanese data alone yields about 1,200 deaths. Use of only the "western" data (Gillis *et al.*, 1984; Garland *et al.*, 1988; Helsing *et al.*) at a constant rate difference yields 7,950 deaths while use of "western" data with the rate difference varying with age yields about 30,000 deaths. Thus, the death calculations using rate differences are quite volatile. Also, it is evident that with the rate differences it is not feasible to carry over the "eastern" experience, in ischemic heart disease at least, for use in a "western" setting. Accordingly, it was concluded that the absolute risk model is not as suited to combining risks for passive smoking as the relative risk models.

Table D2. Regional particle deposition from nose breathing of sidestream smoke.

Aerodynamic diameter μm	Mass distribution %[a]	Fraction of inhaled particle mass deposited[b]				Mass deposited as % of total mass inhaled	
		nose	mouth throat	tracheo-bronchial	alveolar	nose	alveolar
0.20	0.3	0	0	0	0.19	0.00	0.06
0.25	2.4	0.005	0	0	0.172	0.01	0.41
0.30	6.4	0.01	0	0	0.155	0.06	0.99
0.35	13.2	0.015	0	0	0.138	0.20	1.82
0.40	19.6	0.02	0	0	0.12	0.39	2.35
0.45	14.0	0.03	0	0	0.122	0.42	1.70
0.50	15.5	0.04	0	0	0.125	0.62	1.94
0.60	12.7	0.05	0	0	0.128	0.64	1.63
0.70	8.1	0.06	0	0	0.13	0.49	1.05
0.80	6.0	0.077	0	0	0.133	0.46	0.80
0.90	1.7	0.093	0	0	0.137	0.16	0.23
1.00	0.0	0.11	0	0	0.14	0.00	0.00
						3.45	12.99

[a]From Table D1.
[b]From Heyder (1984), Table 2, 250 cm³/second mean flow rate, 4 second breathing cycle.

Table D3. Smoke Particle deposition patterns in direct and passive smoking

	Direct Smoking	Passive Smoking	Direct/Passive
Entry site	Mouth	Nose	
Particulate inhaled per day, mg.	240	2.8	86
Particle Size inhaled, μm	0.7	0.4	
Particle size exhaled, μm	0.7	0.4	
Retained in nose, %	0	3.5	
Retained in mouth, %	25	0	
Retained in tracheo-bronchial region, %	35	0	
Retained in near alveolar region, %	11	0	
Retained in deep alveolar region, %	9	13	
Total retained, %	80	16.5	
Particulate retained, total, mg.	192	0.46	417
Particulate retained, alveolar, mg.	48	0.36	133
Particulate retained, deep alveolar, mg.	22	0.36	61

Appendix D

Dose considerations

As noted in the text, there is a wide difference between the observed disease ratio between passive and active smokers and the ratio of cigarette smoke particulate retained by each. Also, the cancer sites appear to differ. On the assumption that part of these differences may be due to differences in deposition sites between passive smoking and active smoking, calculations were carried out to try to pinpoint these differences.

The calculations for passive smoking are reasonably straightforward. Stöber (1984) has summarized all the uncertainties in this type of calculation. Nevertheless, the best approach appears to be to use the data of Hiller *et al.* (1982) for the particle size range of side stream smoke, centering around 0.4 μm, and the mathematical lung model of Heyder (1984) for inert particles. Integration of these two data sets yields a distribution of deposited weights by particle size for mouth breathing (see Table D1) which, when summed, yields exactly the total deposition observed by Hiller *et al.*, (1982) indicating that the Heyder model holds for passive smoking. The same inhaled particle size distribution can then be applied to Heyder's nose breathing case (see Table D2) which yields nasal deposition of 3.5% and deposition in the alveolar region of the lung of 13.0%. The model predicts zero deposition for both the mouth/throat and the tracheo-bronchial regions. From the deposition curves of Gerrity *et al.* (1979) (Fig. 2) for iron oxide extrapolated to a particle size of 0.25 μm (which is equivalent to an aerodynamic diameter of 0.4 μm) it appears that all of the lung deposition from passive smoking probably occurs deep in the alveolar region at generation 19 or beyond. Black and Pritchard (1984) have determined the half-time for alveolar retention for direct cigarette smoke to be 17 hours indicating that the smoke particles dissolve and clear into the blood or lymph system. There is every reason to believe that the passive smoke particles clear the same way.

With direct smoking there has so far been no model developed that explains the observed phenomena, namely that the inhaled particle size is about 0.7 μm, that 70% to 80% of the inhaled smoke is retained, that 15 to 35% is retained in the mouth, and that the exhaled particle size is also about 0.7 μm. The Heyder model at 0.7 μm would predict total retention of only 12%. To achieve 75% retention, the Heyder model would require an effective particle size of 6.5 μm. Main stream smoke is known to agglomerate, but if it agglomerated to 6.5 μm, the exhaled smoke, according to the Heyder model, would be about 6 μm, much too large compared to that observed. Mitchell (1962) observed that direct smoke particles grow in the mouth to about 1.15 μm and that the smoke exhaled from the lung after a 5 second retention period had a mass median diameter size of 0.65 μm. Let us assume that the 0.65 μm part of the smoke follows Heyder's model and that 20% of the total smoke inhaled was exhaled, all from the 0.65 μm fraction. The inhaled part of the smoke corresponding with the 0.65 μm part exhaled would have the same particle size and would deposit about 12%, deep in the alveolar region. This is 12% of 22.7% of the total smoke inhaled, or 2.7% of the total inhaled smoke. The balance of the inhaled smoke (77%) would have a larger average particle size, about 1.3 μm. Black and Pritchard (1984) found, based on clearance data, that the rates of alveolar deposition to alveolar plus tracheo-bronchial deposition in direct smoking is 0.36. Also, as noted, some amount, say 25% of the total inlet smoke should deposit in the mouth and throat, all of which would have to come from this larger size fraction. Summarizing these numbers, of the 100 − 20 − 25 = 55% of total smoke particulate that reaches the lung and is not exhaled, 0.64 × 55 = 35% deposits in the tracheo-bronchial region and 0.36 × 55 = 20% deposits in the alveolar region. We have already accounted for 3% of the alveolar deposition from the 0.65 μm particles. The remaining 17% would come from the larger particles. Based on the alveolar/tracheo-bronchial split and using the curves of Gerrity *et al.* (1979) it would be expected that about 2/3 of the alveolar deposit or 11% would deposit in the "near" alveolar region, generations 16–18, and 6% in the "deep" alveolar region, generations 19–21, for a total "deep" alveolar deposition of 9%. These calculations are summarized in Table D3.

Just what the mechanisms are for so much direct smoke deposition remains unclear. Certainly impaction and sedimentation (the Heyder model) do not account for it. Stober (1984) suggests that electrical charges in the newly generated smoke particles (see Melandri *et al.*, 1983) may account for some of it. Another possible mechanism is the cloud settling phenomenon as described by Fuchs (1964).

Whatever the mechanism, a reasonably clear idea of the regional deposition patterns from direct and passive smoking

can be obtained as shown in Table D3. The nasal deposition from passive smoking could account for the observed nasal sinus cancer. Also, if the observation of Balin *et al.* (1986) is correct that there is a direct passage for toxics from the nose to the brain, it could also account for the observed brain cancer. In the deep alveolar region the ratio of direct to passive deposition is much closer to the inhaled ratio than to the "total retained" ratio. It is from the deep alveolar region that the smoke particles are solubilized and cleared into the blood and lymph systems possibly to cause cancers of the liver, breast and endocrine glands, leukemia, lymphoma and arterial plaques.